

What is claimed is:

1. An isolated peptide selected from the group consisting of:
  - a) a peptide consisting essentially of SEQ ID NO:2;
  - b) a biologically active fragment of SEQ ID NO:2;
  - c) a peptide consisting essentially of an amino acid sequence that is at least about 70% identical to SEQ ID NO:2, wherein the peptide has the biological activity of SEQ ID NO:2; and
  - d) a peptide consisting essentially of an amino acid sequence that differs from SEQ ID NO:2 by at least one substitution, deletion or insertion of an amino acid residue at a position of SEQ ID NO:2 selected from the group consisting of: 1, 2, 5, 6, 9, 10, 11, 12, 13 and 14, wherein the peptide has the biological activity of SEQ ID NO:2.
2. The isolated peptide of Claim 1, wherein the peptide consists essentially of an amino acid sequence that is at least about 80% identical to SEQ ID NO:2.
3. The isolated peptide of Claim 1, wherein the peptide consists essentially of an amino acid sequence that is at least about 90% identical to SEQ ID NO:2.
4. The isolated peptide of Claim 1, wherein the peptide consists essentially of an amino acid sequence that differs from SEQ ID NO:2 by at least one substitution, deletion or insertion of an amino acid residue at a position of SEQ ID NO:2 selected from the group consisting of: 1, 2, 5, 6, 9, 10, 11 and 12.
5. The isolated peptide of Claim 1, wherein the peptide consists essentially of an amino acid sequence that differs from SEQ ID NO:2 by at least one substitution, deletion or insertion of an amino acid residue at a position of SEQ ID NO:2 selected from the group consisting of: 1, 2, 5, 6, 9, 10 and 11.
6. The isolated peptide of Claim 1, wherein the peptide consists essentially of SEQ ID NO:2.
7. The isolated peptide of Claim 1, wherein the peptide comprises a modification selected from the group consisting of farnesylation, carboxymethylation, geranylgeranylation, and complexing with a lipid carrier.

8. A therapeutic composition comprising the isolated peptide of Claim 1 and a pharmaceutically acceptable carrier.

9. An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

a) a nucleic acid sequence encoding an amino acid sequence consisting essentially of SEQ ID NO:2;

5 b) a nucleic acid sequence encoding a fragment of SEQ ID NO:2 having the biological activity of SEQ ID NO:2;

c) a nucleic acid sequence encoding a peptide consisting essentially of an amino acid sequence that is at least about 70% identical to SEQ ID NO:2;

10 d) a nucleic acid sequence encoding a peptide consisting essentially of an amino acid sequence that differs from SEQ ID NO:2 by at least one substitution, deletion or insertion of an amino acid residue at a position of SEQ ID NO:2 selected from the group consisting of: 1, 2, 5, 6, 9, 10, 11, 12, 13 and 14, wherein the peptide has the biological activity of SEQ ID NO:2; and

15 e) a nucleic acid sequence that is fully complementary to any of the nucleic acid sequences of (a)-(d).

10. The isolated nucleic acid molecule of Claim 9, wherein the nucleic acid sequence is SEQ ID NO:1.

11. A recombinant nucleic acid molecule comprising a nucleic acid sequence as set forth in Claim 9, operatively linked to a recombinant vector.

12. The recombinant nucleic acid molecule of Claim 11, wherein the nucleic acid sequence is operatively linked to a promoter selected from the group consisting of: a cardiac-specific promoter, a muscle-specific promoter, and a prelamin A promoter.

13. A recombinant nucleic acid molecule comprising a nucleic acid sequence operatively linked to a recombinant expression vector for gene delivery selected from the group consisting of:

- a) a nucleic acid sequence encoding SEQ ID NO:4;
- 5        b) a nucleic acid sequence encoding a biologically active fragment of SEQ ID NO:4; and
- c) a nucleic acid sequence encoding an amino acid sequence that is at least about 70% identical to SEQ ID NO:4, wherein the amino acid sequence has prelamins A or lamins A biological activity.

14. A therapeutic protein comprising a protein selected from the group consisting of:

a) a protein comprising an amino acid sequence represented by SEQ ID NO:4;

5 b) a protein comprising biologically active fragment of SEQ ID NO:4; and

c) a protein comprising an amino acid sequence that is at least about 70% identical to SEQ ID NO:4, wherein the protein has prelamin A or lamin A biological activity;

10 wherein the protein is chemically or recombinantly attached to a therapeutic agent that increases the half-life of the protein in cardiac or skeletal muscle tissue.

15. A carrier for therapeutic agents for the treatment of cardiac or skeletal muscle disorders, consisting essentially of an isolated fragment of SEQ ID NO:4 with inter-nuclear transport domain biological activity, or a biologically active homologue thereof.

16. A therapeutic composition for promoting myoblast activation and growth or regeneration of cardiac or skeletal muscle comprising an isolated peptide consisting essentially of the carrier of Claim 15 operatively linked to a therapeutic agent for promoting myoblast activation and growth or regeneration of cardiac or skeletal muscle.

17. A recombinant nucleic acid molecule comprising a nucleic acid sequence encoding the carrier of Claim 15 operatively linked to a nucleic acid sequence encoding a protein for the promotion of myoblast activation and growth or regeneration of cardiac or skeletal muscle.

18. A method to identify compounds that regulate myoblast activation and differentiation, comprising:

a) contacting a cell that expresses a prelamin A protein or a prelamin A pre peptide with a test compound under conditions suitable for modulation of the activity of the prelamin A protein or prelamin A pre peptide by the test compound; and

b) detecting modulation of the activity of the prelamin A protein or prelamin A pre peptide by the test compound.

19. The method of Claim 18, wherein the step of detecting is selected from the group consisting of: detecting whether the test protein regulates prelamin A pre peptide transport in a cell; detecting whether the test protein regulates the processing of prelamin A in a cell; detecting whether the test protein regulates myoblast differentiation; and detecting binding between the prelamin A protein or prelamin A pre peptide and the test compound.

20. The method of Claim 18, wherein the test compound is a protein encoded by a gene that is a candidate for regulation of prelamin A processing or prelamin A pre peptide transport in the cell.

21. The method of Claim 20, wherein the gene is selected from the group consisting of: a human homologue of a gene in the yeast a-type mating pheromone signaling pathway; and a gene encoding a candidate receptor for the prelamin A pre peptide.

22. The method of Claim 18, wherein the cell expressing the prelamin A protein or prelamin A pre peptide is selected from the group consisting of: a differentiating cardiac myocyte or a differentiating skeletal myocyte; a cell that has been transfected with a nucleic acid molecule encoding the prelamin A protein or prelamin A pre peptide; and a prelamin A processing deficient cell.

23. A method to identify compounds that regulate myoblast activation and differentiation, comprising:

a) contacting a prelamin A protein or a prelamin A pre peptide with a test compound under conditions suitable for binding of the prelamin A protein or prelamin A pre peptide by the test compound; and

b) detecting binding of the prelamin A protein or prelamin A pre peptide by the test compound.



24. A method to identify compounds that regulate myoblast activation and differentiation in a cell, comprising:

a) contacting an isolated prelamins A processing-deficient cell with a test compound for regulation of myoblast activation and differentiation; and

b) detecting whether the test compound regulates an activity in the cell selected from the group consisting of: prelamins A processing, prelamins A pre peptide transport, and myoblast activation or differentiation, as compared to in the absence of the test compound.

25. The method of Claim 24, wherein the isolated prelamins A processing-deficient cell is selected from the group consisting of: a cell transfected with a nucleic acid sequence encoding a processing deficient prelamins A protein and a cell that has been isolated from a patient that endogenously expresses a processing-deficient prelamins A protein.

26. The method of Claim 24, wherein the cell is selected from the group consisting of a cardiac myocyte and a skeletal myocyte.

27. The method of Claim 24, wherein the cell is a prelamins A processing deficient cell that has been isolated from a patient, and wherein the cell expresses a prelamins A protein comprising a mutation, with respect to SEQ ID NO:4, selected from the group consisting of: Arg60Gly, Leu85Arg, Glu203Gly, Arg89Leu, Asn19Lys, and Arg377His.

28. The method of Claim 24, wherein the step of detecting is selected from the group consisting of: detecting whether the test compound increases prelamins A processing in the cell as compared to in the absence of the compound; detecting whether the test compound increases prelamins A pre peptide transport in the cell as compared to in the absence of the compound; detecting whether the test compound increases myoblast activation or differentiation in the cell as compared to in the absence of the compound; and detecting an increase in myoblast activation and differentiation in the absence of correcting the prelamins A processing deficiency.

29. The method of Claim 24, wherein the test compound is selected from the group consisting of: a homologue of prelamins A pre peptide with putative prelamins A pre peptide biological activity; a pharmaceutical compound with putative prelamins A pre peptide

biological activity; a homologue of prelamin A with putative prelamin A biological activity;  
5 a candidate protein for a prelamin A processing enzyme, or a gene encoding the candidate  
protein; a candidate protein for a downstream prelamin A pre peptide signal transduction  
protein, or a gene encoding the candidate protein; and a putative pharmaceutical compound  
for use in the treatment of cardiac and skeletal muscle disorders, and wherein an increase in  
the processing of prelamin A in the cell or an increase in myoblast activation and  
10 differentiation in the presence of the compound as compared to in the absence of the  
compound indicates that the compound is a therapeutic compound for use in the treatment  
of cardiac and skeletal muscle disorders.

30. A method to identify human genes that regulate myoblast activation and differentiation, comprising:

a) contacting a probe with a source of human DNA from heart or skeletal muscle tissue under moderate stringency conditions, wherein the probe is a nucleic acid sequence from a gene in the yeast a-type mating pheromone signal transduction pathway;

b) identifying genes in the source of human DNA that hybridize to the probe; and

c) detecting whether genes that hybridize to the probe encode a protein that corrects a prelamin A processing deficiency or that increases myoblast activation and differentiation.

31. The method of Claim 30, wherein the gene in the yeast a-type mating pheromone signal transduction pathway is a gene that is associated with a biological function selected from the group consisting of: transcriptional activation of pheromone responsive genes, post-transcriptional blockade of the cell cycle, and cell fusion pathway activation.

32. A method to identify an inhibitor of prelamin A farnesylation, comprising:  
a) contacting an isolated cell that expresses prelamin A with a putative regulator of prelamin A farnesylation; and

5 b) detecting whether farnesylation of prelamin A is inhibited by the putative regulator.

33. The method of Claim 32, wherein the cell is selected from the group consisting of a differentiating cardiac myocyte and a differentiating skeletal myocyte.

34. The method of Claim 32, wherein the cell has been transfected with a nucleic acid molecule encoding prelamin A.

35. The method of Claim 32, wherein the step of detecting includes detecting whether prelamin A farnesylation is reduced as compared to in the absence of the putative inhibitor compound.

36. The method of Claim 32, further comprising:

5 c) detecting whether inhibitors of prelamin A farnesylation detected in step (b) regulate prelamin A processing in the cell, wherein detection of reduced prelamin A processing in the presence of the regulator indicates that the regulator may be useful for treatment of muscle cell cancers.

37. The method of Claim 32, further comprising:

5 c) detecting whether inhibitors of prelamin A farnesylation detected in step (b) cause myoblast dissociation or myoblast cell death, wherein detection of increased myoblast dissociation or myoblast cell death in the presence of the regulator indicates that the regulator may be useful for treatment of muscle cell cancers.

38. A processing deficient prelamins A peptide, wherein the processing deficient prelamins A peptide consists essentially of an amino acid sequence that differs from SEQ ID NO:4 by at least one substitution, deletion or insertion that results in a decrease in a prelamins A or prelamins A pre peptide biological activity selected from the group consisting of:

- 5 a) prelamins A processing to release a prelamins A pre peptide consisting of SEQ ID NO:2 or a biologically active homologue thereof;
- b) prelamins A pre peptide signal transduction;
- c) synchronization of intercellular signaling with changes in lamins A localization and nuclear lamina morphology that occur early in myoblast differentiation;
- 10 d) synchronization of transcriptional regulation of muscle-specific genes or cell cycle arrest that occurs concomitant with myoblast differentiation;
- e) formation of normal nuclear lamina structure; and
- f) induction of myoblast activation and differentiation.

39. The processing deficient prelamins A peptide of Claim 38, wherein the processing deficient prelamins A peptide consists essentially of an amino acid sequence that differs from SEQ ID NO:4 by a substitution of an amino acid residue in SEQ ID NO:4 selected from the group consisting of: Arg60, Leu85, Glu203, Arg89, Asn195, Arg377, Tyr646, G649, N650, P653, R654, P658, Q659, N660, Cys661, S662, I663 and M664.

40. The processing deficient prelamins A peptide of Claim 38, wherein the substitution is selected from the group consisting of: Arg60Gly, Leu85Arg, Glu203Gly, Arg89Leu, Asn19Lys, and Arg377His.

41. An isolated cell transfected with a processing deficient prelamins A peptide of Claim 38.

42. A method to promote myoblast activation and regeneration of damaged, degenerated or atrophied cardiac and skeletal myocytes, comprising administering to a patient that has damaged, degenerated or atrophied cardiac or skeletal myocytes the isolated peptide of Claim 1, or a composition comprising the peptide.

43. A method to stimulate cardiac or skeletal muscle growth in a mammal, comprising administering to a mammal the isolated peptide of Claim 1, or a composition comprising the peptide.

44. A method to treat cardiac and skeletal muscle disorders, comprising administering to a patient that has a cardiac or skeletal muscle disorder, the therapeutic protein of Claim 14 or a composition comprising the therapeutic protein.

45. The method of Claim 44, wherein said disorder is selected from the group consisting of: dilated cardiomyopathy, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, partial lipodystrophy, axonal neuropathy, and mandibuloacral dysplasia.